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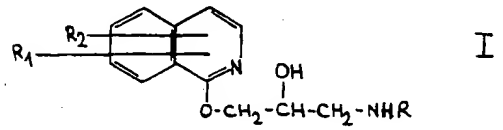
(72) Inventors FRANZ TROXLER and ERIK WISKOTT

(54) IMPROVEMENTS IN OR RELATING TO ISOQUINOLINES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new heterocyclic compounds.

In accordance with the invention there are provided new compounds of formula I,



I

wherein

R is lower alkyl or cycloalkyl of 3 to 7 carbon atoms; cycloalkyl of 3 to 7 carbon atoms substituted by alkyl of 1 to 4 carbon atoms; α-dialkylpropynyl or α-dialkylallyl of 5 to 9 carbon atoms; hydroxyalkyl of 2 to 7 carbon atoms, the hydroxy group thereof being separated by at least two carbon atoms from the nitrogen atom to which R is bound; phenethyl; phenethyl substituted in the ring by halogen, alkyl or alkoxy of 1 to 4 carbon atoms; or adamantyl,

R_1 is hydrogen, halogen, alkyl or alkoxy of 1 to 4 carbon atoms, trifluoromethyl in the 5, 6 or 7 position, or a nitro or A—NH— group in the 4 or 5 position, wherein A is formyl or alkanoyl of 2 to 4 carbon atoms, and

R_2 is hydrogen, or, when R_1 is alkyl of 1 to 4 carbon atoms, also alkyl of 1 to 4 carbon atoms, or, when R_1 is alkoxy of 1 to 4 carbon atoms, also alkoxy of 1 to 4 carbon atoms, with the general proviso that the 8 position of the isoquinoline ring is unsubstituted, and any halogen substituent which may be present in the 3 or 4 position is other than fluorine.

When R is the alkyl or hydroxyalkyl radical defined above, the alkyl moiety is preferably branched, especially in an α position to the nitrogen atom to which it is bound. Specially preferred alkyl moieties are isopropyl, tert. butyl, 3-pentyl and tert.pentyl.

When R is cycloalkyl, this preferably is of 3 to 6 carbon atoms. Examples include cyclopropyl, cyclopentyl and cyclohexyl.

When R is cycloalkyl substituted by alkyl, the alkyl substituent thereof especially signifies methyl. Preferably there is one alkyl substituent. Preferably the substituent is in the 1 position. Examples of interesting alkylcycloalkyl groups are 1-methylcyclopropyl and 1-methylcyclohexyl.

When R is the α-dialkylpropynyl or α-dialkylallyl radical defined above, the alkyl groups thereof preferably are identical and especially signify methyl or ethyl.

When R is a phenethyl group substituted by the radicals defined above, this phenethyl radical especially is mono- or disubstituted. When it is substituted by halogen, halogen signifies fluorine, chlorine or bromine, preferably fluorine or chlorine. Any alkyl or alkoxy substituents of the phenethyl radical preferably contain 1 or 2, especially 1 carbon atom. At least one ring substituent is preferably in the para position.

When R_1 and/or R_2 are alkyl or alkoxy of 1 to 4 carbon atoms, these radicals especially contain 1 or 2, preferably 1 carbon atom.

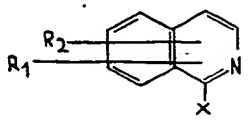
When R, R_1 or R_2 contains halogen, this signifies fluorine, chlorine or bromine, preferably fluorine or chlorine.

Any carbon containing radical not particu-

larly defined herein preferably has up to 5 carbon atoms.

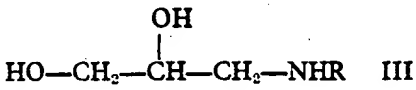
Further, in accordance with the invention a compound of formula I may be obtained by a process comprising

a) reacting a compound of formula II,



II

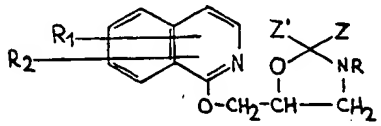
wherein R_1 and R_2 are as defined above, and X is an anionic leaving atom or group, with a compound of formula III,



III

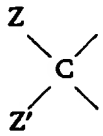
wherein R is as defined above, or

b) hydrolyzing a compound of formula IV,



IV

wherein R, R_1 and R_2 are as defined above, and



is a group capable of being split off during hydrolysis.

The processes of the invention may be effected in a manner analogous to known methods.

The reaction in accordance with process variant

a) may, for example, be effected by allowing to stand a solution of a compound of formula II and a compound of formula III in an inert organic solvent, e.g. a lower alkanol such as ethanol. A basic condensation agent may be present, e.g. an alkali metal alcoholate such as potassium tert.butylate. The reaction temperature may vary between between about 0 and about 80°C, but room temperature is conveniently used. The reaction may be accelerated by stirring. The reaction time depends, inter alia, on the reaction temperature.

X may be, for example, chlorine, bromine or lower alkylthio such as methylthio.

Process variant b) may be effected under conventional conditions for the hydrolysis of oxazolidines. Z and Z' may be chosen such that the moiety Z.CO.Z' is an aliphatic or aromatic ketone or aldehyde. Examples are propionaldehyde, benzaldehyde and acetone. Such oxazolidines may be hydrolyzed under acid conditions.

Suitable acids which may be used are especially dilute acids, e.g. between 0.5 and 3 N, e.g. IN. Mineral acids, e.g. hydrochloric acid or sulphuric acid, may be used.

A convenient reaction temperature is between 0 and about 80°C.

The reaction time depends on the reaction conditions.

The resulting compounds of formula I may be isolated from the reaction mixture and purified in known manner.

Free base forms of compounds may be converted into acid addition salt forms in conventional manner and *vice versa*. Suitable acids for salt formation include organic acids such as maleic acid and fumaric acid and inorganic acids such as hydrochloric acids.

Compounds of formula II wherein X is chlorine or bromine are known or may be produced in a manner analogous to known methods.

Compounds of formula II wherein X is chlorine or bromine may be reacted with hydrogen sulphide to produce corresponding thiol compounds. The reaction may be carried out under conventional conditions, e.g. in methanol. Room temperature is a suitable reaction temperature.

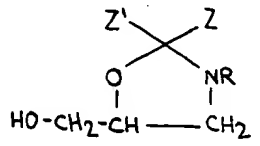
The said thiol compounds may be converted into compounds of formula II, wherein X is alkylthio using conventional alkylation reactions.

A compound of formula III may for example be obtained by reacting 1,2 - dihydroxy - 3 - chloropropane or glycidol with an amine of formula V,

$$H_2NR \qquad V$$

wherein R is as defined above.

A compound of formula IV may be obtained by reacting a compound of formula II with a compound of formula VI,



VI

wherein R is as defined above.

The reaction may be effected in an inert organic solvent. The reaction is conveniently effected in the presence of a base, e.g. potassinum tert.butylate. The reaction temperature may vary between room temperature and a slightly elevated temperature. The reaction may have duration of several hours.

A compound of formula VI may, for example, be obtained by reacting a compound

of formula III with the appropriate aldehyde or ketone.

Insofar as the production of the starting materials is not described, these are known or may be produced in accordance with known processes, or in a manner analogous to the processes described herein or to known processes.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade and are uncorrected.

EXAMPLE 1.

1 - (2 - hydroxy - 3 - isopropylaminopropoxy)- 7 - methoxy - isoquinoline

[process variant b)]

1 g of 1- (3 - isopropyl - 2 - phenyl- 5 - oxazolidinylmethoxy - isoquinoline is heated to 80° in 10 cc of 1 N hydrochloric acid for 10 minutes. The reaction mixture is extracted with ether. The ethereal phase is discarded, and the aqueous phase is made alkaline with potash, extracted with ether, the ether phase is dried over magnesium sulphate and concentrated, whereby a crystalline product is obtained which is treated in methanol with maleic acid. Ether is added, whereby 1- (2 - hydroxy - 3 - isopropylaminopropoxy)- 7 1 methoxyisoquinoline is obtained as hydrogen maleate. M.P. 144—146°.

The 1 - (3 - isopropyl - 2 - phenyl - 5- oxazolidinylmethoxy) - 7 - methoxy - isoquinoline, required as starting material, is obtained as follows:

0.3 g of potassium are dissolved in 15 cc of absolute tert.butanol, and 1.5 g of 1 - chloro- 7 - methoxyisoquinoline and 1.7 g of 5- hydroxymethyl - 3 - isopropyl - 2 - phenyloxazolidine are added. The solution is heated to 50° for 1 hour, whereupon it is evaporated to dryness. The product is digested with water, extracted with ether, the ether phase is dried and the ether is distilled off. 1 - (3 - isopropyl- 2 - phenyl - 5 - oxazolidinylmethoxy) - 7- methoxyisoquinoline is obtained as an oil.

The 5 - hydroxymethyl - 3 - isopropyl - 2- phenyloxazolidine, B.P. 133—134° at 0.08 mm Hg, required for the reaction, is obtained by boiling 1,2 - dihydroxy - 3 - isopropylaminopropane with an excess of benzaldehyde in benzene on a water separator.

1,2 - dihydroxy - 3 - isopropylaminopropane, B.P. 96—98° at 0.4 mm Hg, is obtained by heating 1,2 - dihydroxy - 3 - chloropropane in a 15-fold excess of isipropylamine in a bomb tube to 100°.

EXAMPLE 2.

1 - (2 - hydroxy - 3 - isopropylaminopropoxy)- isoquinoline

[process variant b)]

2.0 g of 1 - (3 - isopropyl - 2 - phenyl - 5- oxazolidinylmethoxy)isoquinoline are heated to 50° for 1 hour with 20 cc of 1 N hydrochloric acid. The reaction mixture is extracted with methylene chloride. The methylene chloride phase is discarded and potash is added to the aqueous phase until an alkaline reaction is obtained, and then extraction is effected thrice with methylene chloride. These three extracts are dried over magnesium sulphate and concentrated. The residue is reacted in tetrahydrofuran with maleic acid to obtain 1 - (2- hydroxy - 3 - isopropylaminopropoxy)- isoquinoline hydrogen maleate having an M.P. of 166—167°.

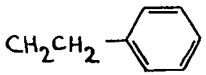
EXAMPLE 3.

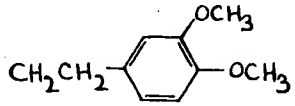
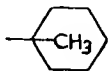
1 - (2 - hydroxy - 3 - isopropylaminopropoxy)- 6 - methoxy - isoquinoline

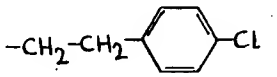
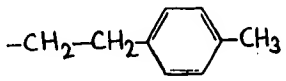
[process variant b)]

25 cc of 1 N hydrochloric acid are added to 3.0 g of 1 - (3 - isopropyl - 2 - phenyl- 5 - oxazilidinylmethoxy) - 6 - methoxy - isoquinoline, and the mixture is stirred at room temperature for 2 hours. Working up is effected in a manner analogous to that described in Example 1. 1 - (2 - hydroxy - 3 - isopropylaminopropoxy) - 6 - methoxy - isoquinoline, having an M.P. of 95—97°, is obtained.

The following compounds of formula I are obtained in a manner analogous to that described in Examples 1 to 3 by a ring opening in the corresponding 1 - (5 - oxazolidinylmethoxy)isoquinolines:

Example	R	R_1	R_2	M.P.	
4	$CH(CH_3)_2$	5–CH_3O	H	(hydrogen maleate)	158–160°
5	$CH(CH_3)_2$	3–CH_3	H	(hydrogen maleate)	150–151°
6	$CH(CH_3)_2$	7–CH_3	H	(hydrogen maleate)	164–168°
7	$CH(CH_3)_2$	4–CH_3	H	(hydrogen maleate)	139–140°
8		H	H	(hydrogen maleate)	178–180°
9	$C(CH_3)_3$	H	H	(hydrogen maleate)	180°
10	adamantyl	H	H	(hydrogen maleate)	166–167°
11	CH_2=$CH(CH_3)_2$	H	H	(hydrogen maleate)	178–180°
12	CH_2=$C(CH_3)_3$	H	H	(hydrogen maleate)	115–117°
13		H	H	(hydrochloride)	121–123°
14	$CH(CH_3)_2$	6–CH_3O	7–CH_3O	(base)	98–100°
15	$C(CH_3)_3$	4–CH_3O	H	(base)	134–136°
16	$CH(CH_3)_2$	7–Cl	H	(hydrogen maleate)	160–163°
17	$CH(CH_3)_2$	7–$CH(CH_3)_2$	H	(hydrogen maleate)	141–143°
18	$CH(CH_3)_2$	7–CF_3	H	(hydrogen maleate)	171–173°

Example	R	R_1	R_2	M.P.	
19		H	H	(bis[base]fumarate)	
20	$C(CH_3)_2-C\equiv CH$	H	H	(bis[base]fumarate)	176–177°
21	$CH(CH_3)_2$	5–NO_2	H	(hydrogen maleate)	155–157°
22	$CH(CH_3)_2$	5–$NHCOCH_3$	H	(base)	153–55°
23		H	H	(bis[base]fumarate)	168–69°
24	$C(CH_3)_2C_2H_5$	H	H	(hydrogen maleate)	151–53°
25	$C(CH_3)_2CH=CH_2$	H	H		
26	$C(CH_3)_2CH_2OH$	H	H	(bis[base]naphthalene-1,5-disulphonate)	168–171°
27	$C(CH_3)_3$	7–Cl	H	(hydrogen maleate)	200–202°
28	$C(CH_3)_3$	7–CH_3O	H	(hydrogen maleate)	190–192°
29	$C(CH_3)_3$	7–F	H		
30	$CH(CH_3)_2$	7–Br	H		
31		H	H		

Example	R	R_1	R_2	M.P.
32		H	H	
33		H	H	
34	$C(CH_3)_3$	5–NHCHO	H	
35	$C(CH_3)_3$	5–CH_3	7–CH_3	
36	$C(CH_3)_3$	3–CH_3	6–CH_3	
37	$-C(C_2H_5)_2C{\equiv}CH$	H	H	Bis(base)fumarate 148–9°

EXAMPLE 38.

1 ([2 - hydroxy - (2 - methyl - 3 - butyn-2 - ylamino) - propoxy)isoquinoline [process variant a)]

[process variant a)]

0.86 g of potassium are dissolved in 40 cc of tert.butyl alcohol, and 3.8 g of 1 (2-methyl - 3 - butynylamino) - 2,3 - dihydroxypropane and then 3.6 g of 1-chloroisoquinoline are added. After stirring for one day, heating is effected to 50° for a further day. The reaction solution is concentrated in a vacuum. The residue is taken up in 1 N hydrochloric acid and ether, the aqueous phase is neutralized with a 2 N soda solution and extracted with methylene chloride. After drying over magnesium sulphate and concentrating, an oil is obtained which gives the bis-fumarate of the title compound, having an M.P. of 176—177°, with fumaric acid in methylene chloride and ether.

The required 1 - (2 - methyl - 3 - butynylamino) - 2,3 - dihydroxypropane is obtained by reaction of glycidol with an equimolar amount of 2 - amino - 2 - methyl - 3 - butyne in ethanol.

The compounds of formula I described in Examples 1 to 24 and 26 to 37 are obtained in a manner analogous to that described in Example 38 by reacting the corresponding compound of formula II with the corresponding compound of formula III, using process variant a).

The compounds of formula I exhibit pharmacological activity. In particular, the compounds exhibit a blocking effect on the adren-

ergic β receptors (a β-blocking effect) as indicated in standard tests, for example, by an inhibition of the positive inotropic adrenaline effect in the spontaneously beating, isolated guinea-pig atrium.

The compounds are therefore indicated for use as β-blocking agents. Such agents are indicated for use *inter alia* in the propylaxis and therapy of coronary diseases, especially in the treatment of Angina pectoris, in the treatment of the hyperkinetic heart syndrome and the conditions resulting from a muscular hypertrophic subvalvular aortic stenosis. Owing to the β-blocking effect the compounds are further indicated to exhibit an antiarrhythmic effect for use in the treatment of heart rhythm disorders.

An indicated daily dose is from about 2 to about 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.5 to about 250 mg, or in sustained release form.

Additionally, the compounds inhibit the increase in free fatty acid concentration due to mobilisation, and lipolysis, in blood induced by emotional stress as indicated in standard tests, for example, by an inhibition of glycerol release stimuated by isoproterenol *in vitro* in isolated fat cells of epididymal fat tissue of rats, the cells having been isolated in accordance with this method of M. Rodbell [J. biol. chem. *239*, 375—80 (1964)], and *in vivo* in rats.

The compounds are therefore further indicated for use as inhibitors of hyperlipoidemia induced by emotional stress, and therefore possibly for use in the treatment or prophylaxis of myocardism.

For this use an indicated daily dose is from about 1 to about 200 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.25 to about 100 mg, or in sustained release form.

Additionally, the compounds inhibit the increase in glucose concentration in the blood induced by emotional stress as indicated in standard tests, e.g. by an inhibition of glucose release stimulated by isoproterenol *in vivo* in the rat.

The compounds are therefore furthermore indicated for use as inhibitors of hyperglycemia induced by emotional stress and as suppressants of appetite induced by emotional stress.

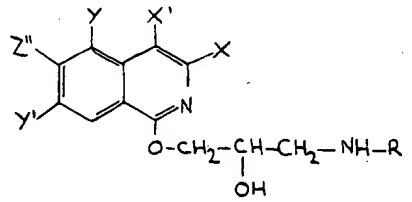
For this use an indicated daily dose is from about 1 to about 200 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.25 to about 100 mg, or in sustained release form.

Especially suitable for the latter use are compounds of formula I wherein R is a radical branched in an α-position to the nitrogen atom to which R is bound; especially interesting are compounds of formula I whereein R is bound to the nitrogen atom with a tertiary carbon atom.

The compounds of Examples 2, 9, 16, 20 and 27 are especially interesting compounds.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order or activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

A group of compounds have the formula



wherein

i) each of X, X', Y, Y' and Z'' are hydrogen,

or

ii) one of X, X', Y and Y' is methyl and the others of X, X, Y and Y' together with Z'' are hydrogen,

or

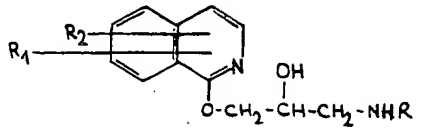
iii) one of Y, Y' and Z'' is methoxy and the others of Y, Y' and Z'' together with X and X' are hydrogen, and

R is alkyl, cycloalkyl or phenethyl.

In another group R_2 is in the 6 or 7 position.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



I

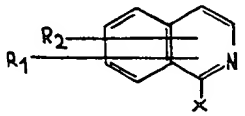
wherein

R is lower alkyl or cycloalkyl of 3 to 7 carbon atoms; cycloalkyl of 3 to 7 carbon atoms substituted by alkyl of 1 to 4 carbon atoms; α-dialkylpropynyl or α-dialkylallyl of 5 to 9 carbon atoms; hydroxyalkyl of 2 to 7 carbon atoms, the hydroxy group thereof being separated by at least two carbon atoms from the nitrogen atom to which R is bound; phenethyl; phenethyl substituted in the ring by halogen, alkyl or alkoxy of 1 to 4 carbon atoms; or adamantyl,

R_1 is hydrogen, halogen, alkyl or alkoxy of 1 to 4 carbon atoms, trifluoromethyl in the 5, 6 or 7 position, or a nitro or A—NH— group in the 4 or 5 position, wherein A is formyl or alkanoyl of 2 to 4 carbon atoms, and

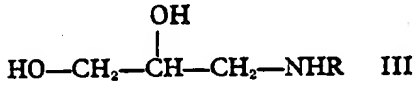
R_2 is hydrogen, or, when R_1 is alkyl of 1 to 4 carbon atoms, also alkyl of 1 to 4 carbon atoms, or, when R_1 is alkoxy of 1 to 4 carbon atoms, also alkoxy of 1 to 4 carbon atoms, with the general proviso that the 8 position of the isoquinoline ring is unsubstituted, and any halogen substituent which may be present in the 3 or 4 position is other than fluorine,

a) reacting a compound of formula II,



II

wherein R_1 and R_2 are as defined above, and X is an anionic leaving or atom group, with a compound of formula III,

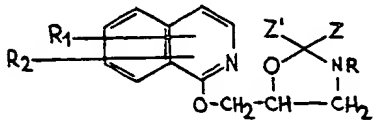


III

wherein R is as defined above,

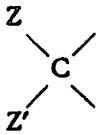
or

b) hydrolyzing a compound of formula IV,



IV

wherein R, R_1 and R_2 are as defined above, and



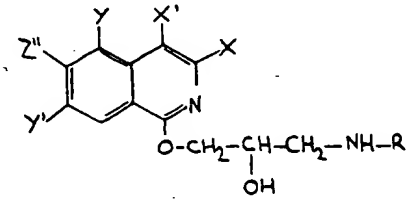
is a group capable of being split off during hydrolysis.

2. A process for the production of a compound of formula I, as stated in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

3. A compound of formula I, whenever produced by a process according to claim 1 or 2.

4. A compound of formula I, as defined in claim 1.

5. A compound of claim 4 having the formula,



wherein

i) each of X, X', Y, Y' and Z'' are hydrogen,

or

ii) one of X, X', Y and Y' is methyl and the others of X, X', Y and Y' together with Z'' are hydrogen,

or

iii) one of Y, Y' and Z'' is methoxy and the others of Y, Y' and Z'' together with X and X' are hydrogen, and

R is alkyl, cycloalkyl or phenethyl.

6. A compound of claim 5, wherein R is isopropyl.

7. A compound of claim 3, 4, 5 or 6, wherein R is a radical branched in the α position to the nitrogen atom to which R is bound.

8. A compound of claim 7 wherein R is bound to the nitrogen atom with a tertiary carbon atom.

9. The compound of claim 4, which is 1-(2 - hydroxy - 3 - isopropylaminopropoxy)-7 - methoxy - isoquinoline.

10. The compound of claim 4, which is 1-(2 - hydroxy - 3 - isopropylaminopropoxy)-isoquinoline.

11. The compound of claim 4, which is 1-(2 - hydroxy - 3 - isopropylaminopropoxy)-6 - methoxy - isoquinoline.

12. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 5—CH_2O, H.

13. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 3—CH_3, H.

14. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 7—CH_3, H.

15. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 4—CH_3, H.

16. The compound of claim 4, wherein R, R_1 and R_2 are respectively

H, H.

17. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, H, H.

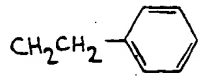
18. The compound of claim 4, wherein R, R_1 and R_2 are respectively adamantyl, H, H.

19. The compound of claim 4, wherein R, R_1 and R_2 are respectively CH_2—$CH(CH_3)_2$, H, H.

20. The compound of claim 4, wherein R,

R_1 and R_2 are respectively CH_2—$C(CH_3)_3$, H, H.

21. The compound of claim 4, wherein R, R_1 and R_2 are respectively



H, H.

22. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 6—CH_3O, 7—CH_3O.

23. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 4—CH_3O, H.

24. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 7—Cl, H.

25. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 7—$CH(CH_3)_2$, H.

26. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 7—CF_3, H.

27. The compound of claim 4, wherein R, R_1 and R_2 are respectively

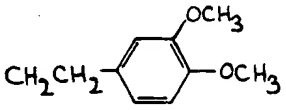
H, H

28. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_2$—C≡CH, H, H.

29. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 5—NO_2, H.

30. The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 5—$NHCOCH_3$, H.

31. The compound of claim 4, wherein R, R_1 and R_2 are respectively



H, H.

32. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_2C_2H_5$, H, H.

33. The compound of claim 4, wherein R, R_1 and R_2 are respectively

$C(CH_3)_2CH=CH_2$, H, H.

34. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_2CH_2OH$, H, H.

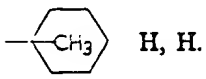
35. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 7—Cl, H.

36. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 7—CH_3O, H.

37. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 7—F, H.

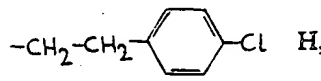
38 The compound of claim 4, wherein R, R_1 and R_2 are respectively $CH(CH_3)_2$, 7—Br, H.

39. The compound of claim 4, wherein R, R_1 and R_{12} are respectively



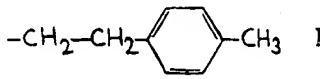
H, H.

40. The compound of claim 4, wherein R, R_1 and R_2 are respectively



H, H.

41. The compound of claim 4, wherein R, R_1 and R_2 are respectively



H, H.

42: The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 5—NHCHO, H.

43. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 5—CH_3, 7—CH_3.

44. The compound of claim 4, wherein R, R_1 and R_2 are respectively $C(CH_3)_3$, 3—CH_3, 6—CH_3.

45. The compound of claim 4, wherein R, R_1 and R_2 are respectively

—$C(C_2H_5)_2C$≡CH, H, H.

46. A compound according to any one of claims 3 to 45 in free base form.

47. A compound according to any one of claims 3 to 45 in acid addition salt form.

48. A pharmaceutical composition comprising a compound according to any one of claims 3 to 45 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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